Unusual Retention of Isoxazole Ring under the Influence of 3-(Substituted nitrophenyl)-2-Isoxazoline during Catalytic Hydrogenation of Isoxazoline-Substituted Isoxazole Systems

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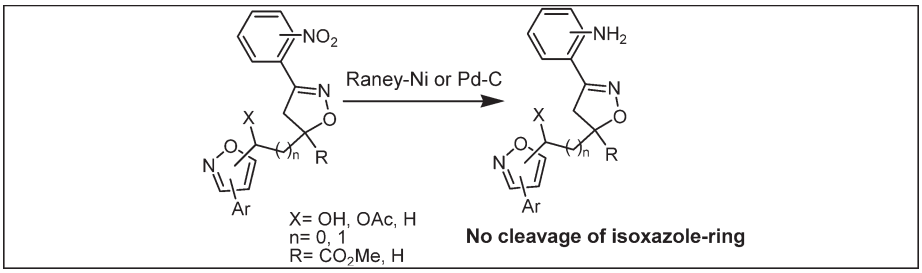
Dedicated to Professor Raymond C. F. Jones on the occasion of his 60th birthday.



The cleavage of the isoxazole ring during the Raney-Ni-promoted catalytic hydrogenation is prevented under the influence of 3-(substituted nitrophenyl)-2-isoxazoline in isoxazoline-substituted isoxazole systems produced *via* 1,3-dipolar cycloaddition either on the Baylis–Hillman derivatives or Grignard products. Unexpectedly, the hydrogenations in these diastereomeric compounds were observed to exclusively yield products, wherein the methoxycarbonyl and the hydroxyl or the acetyl groups exist *syn* to each other.

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INTRODUCTION

The catalytic hydrogenation of isoxazole and 2-isoxazoline heterocyclic systems in the presence of heterogeneous catalysts is relatively old and well-studied subject of synthetic organic chemistry [1]. Recently, we have discovered that the 2-isoxazoline system containing a 2-,3- or 4-nitrophenyl group at 3-position does not undergo ring cleavage under catalytic hydrogenation [2]. In our program to carry out Baylis–Hillman reaction-assisted synthesis of cyclic compounds [3], based on the aforementioned observation, we envisaged the synthesis of the spiroisoxazoline **III** from **I** (Figure 1). Substrate **I** was to be readily generated *via* 1,3-dipolar cycloaddition of appropriate benzonitrile oxide on the Baylis–Hillman adduct of substituted 3-isoxazolecarbaldehyde. In principle, a Raney-Ni-promoted hydrogenation would result in chemoselective ring cleavage of **I** to afford **II**, which may undergo intramolecular cyclization to produce the spiro-derivative. Spiroisoxazoline class of compounds has stimulated great interest in medicinal and biological chemistry [4]. Moreover, naturally occurring spiroisoxazolines have been found useful in different biomedical areas [5].

Therefore, we initiated the investigation by synthesizing **I** *via* 1,3-dipolar cycloaddition of the nitro-substituted benzonitrile oxide to the Baylis–Hillman adduct of 3-isoxazolecarbaldehyde and subjecting it to catalytic hydrogenation in the presence of Raney-Ni. Unexpectedly, analysis of the product isolated after work-up of the reaction revealed that instead of cleavage of the isoxazole ring, only the nitro group present on the phenyl group of the isoxazoline ring was reduced to amino group. A careful literature survey revealed that several reports described the Pd-on-carbon-promoted hydrogenation of the isoxazole derivatives without cleavage of the ring [6], but there exists no report exemplifying the retention of the isoxazole ring during Raney-Ni-promoted catalytic hydrogenation. This prompted us to systematically investigate the catalytic hydrogenation of derivatives wherein the isoxazole ring carry 3-(substituted nitrophenyl)-2-isoxazoline as substituent. It was observed that the cleavage of the isoxazole ring was invariably prevented during the catalytic hydrogenation because of the influence of 3-(substituted nitrophenyl)-2-isoxazoline in an isoxazoline-substituted isoxazole derivative. The details of this study are presented in this communication.

RESULTS AND DISCUSSION

The Baylis–Hillman adducts (**1a–c**) of substituted 3-isoxazolecarbaldehydes were prepared according to the

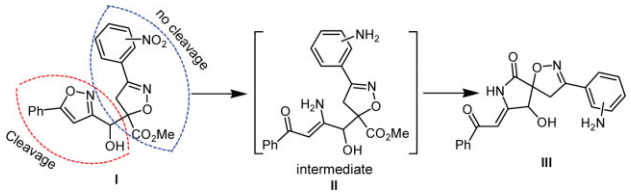
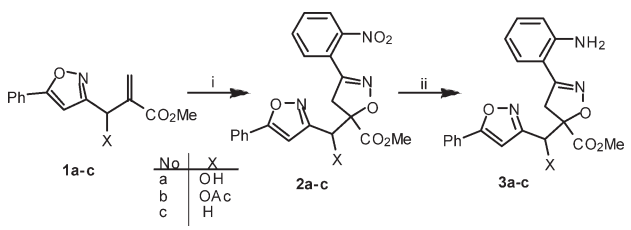


Figure 1. Possible route to spiroisoxazoline from isoxazoline-substituted isoxazole system. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

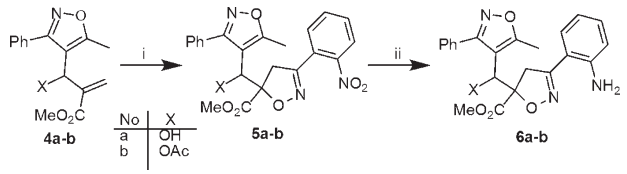
literature procedure [7] and subjected to 1,3-dipolar cycloaddition with 2-nitrobenzonitrile oxide. The required benzonitrile oxide was generated *in situ* from corresponding 2-nitrophenyl methylhydroximinoyl chloride by treating it with triethyl amine in dry ether. This reaction yielded **2a–c** as diastereomeric mixtures (1:1) in 78–83% yields. Hydrogenation of **2a** in the presence of Raney-Ni in methanol on a Parr assembly led to completion of reaction in 3 h. Unexpectedly, the spectral analysis of the isolated product (67% yield) led us to establish the structure as **3a** as a single diastereomer (Scheme 1). At this stage, the likelihood was that both the diastereomer were formed during the reaction, but we isolated only one of them. Consequently, ^{1}H NMR of the crude product was recorded. This spectrum also indicated the presence of a single diastereomer. Assuming that the period of reaction was insufficient to affect the cleavage of the isoxazole ring, the hydrogenation was repeated by continuing it for longer duration (*ca.* 24 h). The product isolated even after 24 h of the reaction time, however, was found to be **3a**. This led us to examine the hydrogenation using Pd-on-carbon as the catalyst. Interestingly, under this condition too, the compound **2a** was transformed to **3a** in 65% yield. To evaluate the outcome of these reactions with other substrates, compounds **2b** and **2c** were subjected to similar reactions. Both substrates behaved in an identical fashion to furnish corresponding products **3b** and **3c** as a single diastereomer in 63–66% yields.

This unusual observation generated interest to study hydrogenation in similar substrates afforded from the Baylis–Hillman adducts of substituted 4- and 5- isoxazole-carbaldehydes [8,9]. Accordingly, compounds **5a,b** were prepared in 83–92% yields from the Baylis–Hillman adduct **(4a)** of 3-phenyl-5-methyl-4-isoxazolecarbaldehyde and corresponding acetate **4b** through 1,3-dipolar cycloaddition. These compounds upon hydrogenation in the presence of Raney-Ni resulted in **6a,b** (Scheme 2) as single diastereomer in 66–92% yields. The relative stereochemistry delineated *via* X-ray crystallographic analysis of a single crystal of compound **6b** indicated that the acetyl group is placed *syn* to the ester group (Figure 2) [10].

Scheme 1. Reagents and conditions: (i) (2-$NO_2C_6H_4$)—C(=NOH)Cl, Et_3N, Et_2O, −78°C to rt, 12 h. (ii) Raney-Ni or Pd on carbon, H_2, MeOH, rt, 40 psi, 3 h.



Scheme 2. Reagents and conditions: (i) (2-$NO_2C_6H_4$)—C(=NOH)Cl, Et_3N, Et_2O, −78°C to rt, 12 h. (ii) Raney-Ni, H_2, MeOH, rt, 40 psi, 3 h.



In the next stage, the Baylis–Hillman derivatives **7a–c** and **8a** afforded from substituted 5-isoxazolecarbaldehydes were subjected to the cycloaddition with 2-nitrobenzonitrile oxide to furnish **9a–c** and **10a**, respectively, as diastereomeric mixtures (1:1) in 82–89% yields. Hydrogenation of **9a–c** and **10a** in the presence of Raney-Ni yielded **13a–c** and **14a**, respectively, in 63–71% yields (Scheme 3).

Next, to investigate whether the position of the nitro group in the phenyl ring has any effect on the outcome of the product, we prepared compounds **11a** and **12a** and carried out Raney-Ni-promoted hydrogenation.

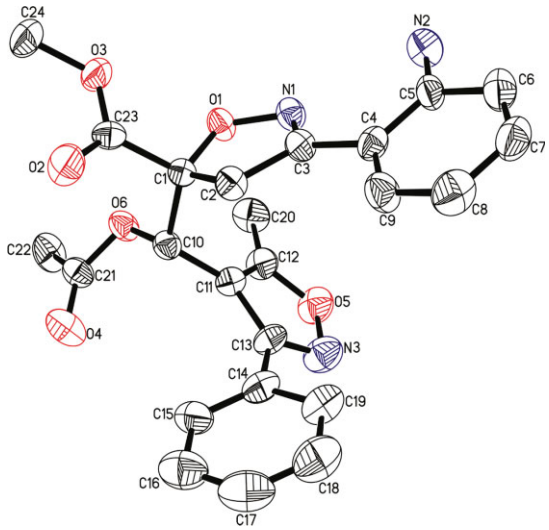
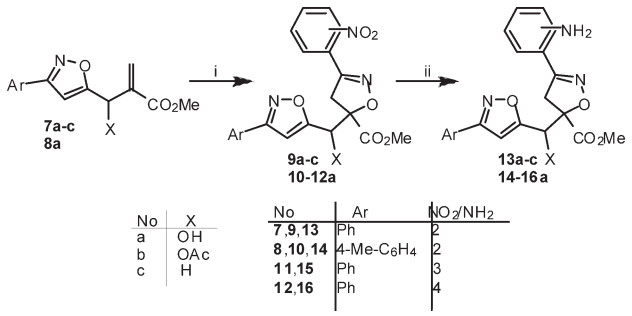


Figure 2. Ortep diagram of compound **6b** showing retention of both isoxazole and isoxazoline ring during catalytic hydrogenation [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

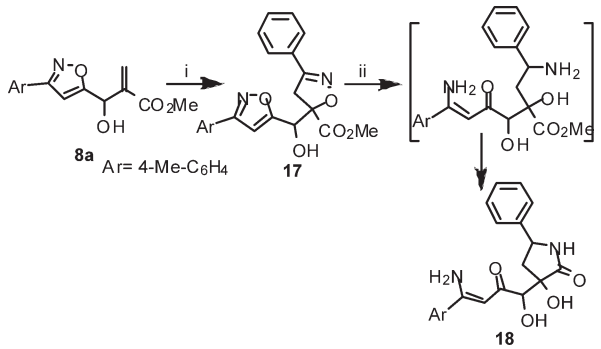
Scheme 3. Reagents and conditions: (i) (2,3 or 4-$NO_2C_6H_4$)—C(=NOH)Cl, Et_3N, Et_2O, −78°C to rt, 12 h. (ii) Raney-Ni or Pd on carbon, H_2, MeOH, rt, 40 psi, 3–5 h.



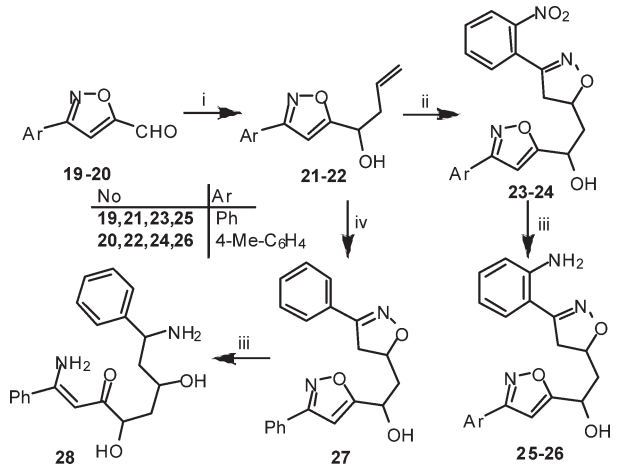
Gratifyingly, these substrates were also transformed to products **15a** and **16a**. In the absence of evidence, it is difficult to comment on the observed stereoselectivity; it is assumed that during hydrogenation reaction, inversion of one of the diastereomer occurs to produce the product with syn-stereochemistry only.

Earlier, we have observed that replacing the nitro-substituted phenyl with phenyl group at 3-position of the 2-isoxazoline makes it prone to ring cleavage during the catalytic hydrogenation [2]. In view of this observation, we decided to evaluate the effect of catalytic hydrogenation in the system where the nitrophenyl group was replaced by phenyl group. Hence, in a model study, compound **17** was prepared from reaction between compound **8a** and benzonitrile oxide. The Raney-Ni-mediated hydrogenation of **17** yielded a product, which was analyzed to be the 2-pyrrolidone **18** (Scheme 4). The formation of compound **18** from **17** implied that during catalytic hydrogenation, cleavage of both the isoxazole and the 2-isoxazoline rings ensued. This result made it apparent that presence of a nitro-substituted phenyl moiety at the 3-position of the 2-isoxazoline protected the isoxazole from ring cleavage during the catalytic hydrogenation of an isoxazoline-substituted isoxazole system.

Scheme 4. Reagents and conditions: (i) C_6H_5—C(=NOH)Cl, Et_3N, Et_2O, −78°C to rt, 12 h. (ii) Raney-Ni, H_2, MeOH, rt, 40 psi, 3 h.



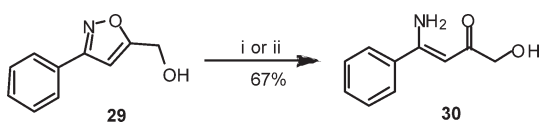
Scheme 5. Reagent and conditions: (i) allyl bromide, Mg, Et_2O, rt, 3 h. (ii) (2-NO_2)C_6H_4C(=NOH)Cl, Et_3N, Et_2O, −78°C, 12 h. (iii) Raney-Ni, H_2, rt, 40 psi, 3–5 h. (iv) C_6H_5C(=NOH)Cl, Et_3N, Et_2O, −78°C, 12 h.



With the objective to find whether this phenomenon was restricted to the system wherein both the rings were separated by a methylene bridge or extend to a system wherein the two rings are separated by ethylene spacer compounds **23–24** were prepared. Grignard reaction of **19–20** with allylbromide resulted in the formation of **21–22** in good yields (Scheme 5). 1,3-Dipolar cycloaddition reaction of 2-nitrobenzonitrile oxide on the double bond of the allyl moiety furnished the required derivatives **23–24**. Hydrogenation of compounds **23–24** in the presence of Raney-Ni in methanol at room temperature in the Parr assembly yielded compounds **25–26**, respectively. Simultaneously, 1,3-dipolar cycloaddition of benzonitrile oxide on **21** was accomplished to afford the product **27**. As expected, hydrogenation of **27** in the presence of Raney-Ni at room temperature for 3 h led to the cleavage of isoxazole and isoxazoline ring leading to **28**. This study further substantiate that the presence of a 2-isoxazoline ring bearing a nitro-phenyl substitution at 3-position protect the isoxazole ring from hydrogenolysis.

On suggestion from one of the reviewers that the production of aniline derivatives during the hydrogenation would be poisoning the catalyst to prevent further reaction, hydrogenations of different substrates in the presence of aniline were investigated. Hydrogenating a simpler isoxazole derivative **29** in the presence of aniline

Scheme 6. Reagent and conditions: (i) Aniline, Raney-Ni, H_2, rt, 40 psi, 5 h. (ii) Aniline, Raney-Ni, H_2, rt, 40 psi, 1 h then added **29**, 5 h.



and Raney-Ni furnished **30** in 67% yield (Scheme 6). Alternatively, a mixture of aniline and Raney-Ni was maintained under hydrogen atmosphere for 1 h followed by addition of **29**. This reaction too resulted in the formation of **30** in 5 h. Similar study was also performed with compound **27**. Here too, the hydrogenolyzed product **28** was isolated in 62% yield. This study delineated that the presence of aniline in the hydrogenation mixture does not affect the activity of the catalyst.

CONCLUSIONS

In summary, we have disclosed an interesting observation wherein the cleavage of the isoxazole ring during the catalytic hydrogenation is influenced by the substitutions present on the 3-position of the 2-isoxazoline ring in isoxazoline-substituted isoxazole systems. Further work toward exploring applications of the intermediates resulting from the study for the synthesis of heterocyclic systems is underway.

EXPERIMENTAL

Melting points are uncorrected and were determined in capillary tubes on an apparatus containing silicon oil. IR spectra were recorded using Perkin Elmer's Spectrum RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker DPX-200 FT or Bruker Avance DRX-300 spectrometers, using TMS as an internal standard (chemical shifts in δ values, *J* in Hz). The ESMS were recorded on MICROMASS LCMS system and FABMS were recorded on JEOL/ SX-102 spectrometer. Elemental analyses were performed on Carlo Erba's 108 or Elementar's Vario EL III microanalyzer. The HRMS spectra were recorded as EI-HRMS. Compounds **2, 5, 9–12** existed as 1:1 diastereomeric mixtures.

General procedure for the synthesis of compounds 2a–c, 5a–b, 9a–c, 10–12a, 17, 23–24, and 27: as exemplified for the compound 2a. To a stirred solution of compound **1a** (2.0 g, 7.7 mmol) and 2-nitrophenyl methylhydroximinoyl chloride (1.85 g, 9.3 mmol) in anhydrous diethylether (15 mL) was added dropwise a solution of Et_3N (1.5 mL, 11.1 mmol) in anhydrous diethylether (5 mL) at −78°C. The reaction was allowed to continue at room temperature for 24 h. Thereafter, the reaction mixture was quenched with water (30 mL) and the ether layer was separated. The aqueous layer was again extracted with diethylether. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated to obtain the crude oily residue. The crude product was then purified by column chromatography over silica gel (60–120 mesh) using hexane/ethyl acetate (70:30, v/v) as the eluent to afford 2.58 g (79%) of **2a** as a brown solid.

Methyl 5-[hydroxy-(5-phenylisoxazol-3-yl)-methyl]-3-(2-nitrophenyl)-4,5-dihydro-isoxazole-5-carboxylate (2a). Mp 120–122°C, IR (potassium bromide): 1741 (CO_2Me), 3449 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.69 (d, 1H, 1H of CH_2, J = 17.7 Hz), 3.81–3.93 (m, 9H, CH_2, 1H of CH_2 and 2 × CO_2CH_3), 5.49 (d, 1H, C*H*OH, J = 5.8 Hz), 5.56 (s, 1H, C*H*OH), 6.74 (s, 1H, =CH), 6.77 (s, 1H, =CH), 7.45–7.46 (m, 8H, 2 × 4ArH), 7.60–7.68 (m, 4H, 2 × 2ArH), 7.80–7.81 (m, 4H, 2 × 2ArH), 8.06–8.11 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 42.5, 43.3, 53.9, 69.2, 90.5, 91.8, 99.4, 124.6, 124.8, 125.3, 126.3, 127.4, 128.4, 128.8, 129.4, 130.8, 131.0, 131.5, 134.0, 134.9, 148.1, 156.6, 162.8, 170.0, 170.9; ms: (electron spray+) *m*/*z* 424.2 (M^+ + 1). *Anal*. Calcd for $C_{21}H_{17}N_3O_7$: C, 59.57; H, 4.05; N, 9.93. Found: C, 59.48; H, 4.11; N, 9.98.

Methyl 5-[acetoxy-(5-phenylisoxazol-3-yl)-methyl]-3-(2-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (2b). This compound was obtained in 83% yield as a white solid, mp 133–135°C; IR (potassium bromide): 1756 (CO_2Me and OAc) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.22 (s, 3H, $OCOCH_3$), 2.25 (s, 3H, $OCOCH_3$), 3.80–4.01 (m, 10H, 2 × CH_2 and 2 × CO_2CH_3), 6.67 (s, 1H, =CH), 6.68 (s, 1H, =CH), 7.40–7.49 (m, 8H, 2 × 3ArH and 2 × CHOAc), 7.60–7.68 (m, 6H, 2 × 3ArH), 7.79–7.86 (m, 4H, 2 × 2ArH), 8.07–8.13 (m, 2H, 2 × 1ArH); ^{13}C NMR (deuteriochloroform): δ 21.1, 21.3, 42.6, 43.3, 54.0, 54.2, 67.8, 89.3, 90.0, 102.9, 103.7, 124.6, 124.7, 125.4, 127.1, 127.4, 128.7, 128.9, 129.4, 130.5, 130.7, 131.6, 134.0, 134.2, 148.1, 156.2, 156.3, 163.1, 166.1, 166.3, 168.2, 168.8, 169.5, 169.9, 171.2; ms: (electron spray+) *m*/*z* 466.1 (M^+ + 1). *Anal*. Calcd for $C_{23}H_{19}N_3O_8$: C, 59.36; H, 4.11; N, 9.03. Found: C, 59.13; H, 4.21; N, 8.96.

Methyl 3-(2-nitrophenyl)-5-(5-phenylisoxazol-3-ylmethyl)-4,5-dihydroisoxazole-5-carboxylate (2c). This compound was obtained in 78% yield as yellow oil; IR (neat): 1744 (CO_2Me) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.47 (d, 1H, 1H of CH_2, J = 17.4 Hz), 3.66 (d, 2H, CH_2, J = 6.1 Hz), 3.86 (d, 1H, 1H of CH_2, J = 17.4 Hz), 3.93 (s, 3H, CO_2CH_3), 6.63 (s, 1H, =CH), 7.45–7.50 (m, 3H, ArH), 7.61–7.71 (m, 3H, ArH), 7.81–7.84 (m, 2H, ArH), 8.10 (d, 1H, ArH, J = 7.2 Hz); ^{13}C NMR (deuteriochloroform) δ= 33.5, 45.5, 53.7, 87.8, 102.6, 124.3, 124.5, 125.1, 127.0, 128.8, 129.0, 130.2, 131.2, 133.9, 147.7, 155.9, 162.9, 167.1, 167.2, 170.2; ms: (electron spray+) *m*/*z* 408.1 (M^+ + 1). *Anal*. Calcd for $C_{21}H_{17}N_3O_6$: C, 61.91; H, 4.21; N, 10.31. Found: C, 61.78; H, 4.29; N, 10.26.

Methyl 5-[hydroxy-(5-methyl-3-phenylisoxazol-4-yl)-methyl]-3-(2-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (5a). This compound was obtained in 92% yield as pale yellow oil; IR (neat): 1744 (CO_2Me), 3382 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.64 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 3.07 (d, 1H, 1H of CH_2, J = 17.4 Hz), 3.36 (d, 1H, 1H of CH_2, J = 17.4 Hz), 3.45 (d, 1H, 1H of CH_2, J = 17.4 Hz), 3.53 (d, 1H, 1H of CH_2, J = 17.4 Hz), 3.61 (s, 6H, 2 × CO_2CH_3), 5.26 (s, 1H, C*H*OH), 5.40 (s, 1H, C*H*OH), 7.21–7.42 (m, 2H, 2 × 1ArH), 7.43–7.57 (m, 10H, 2 × 5ArH), 7.60–7.69 (m, 4H, 2 × 2ArH), 8.02–8.07 (m, 2H, 2 × 1ArH); ^{13}C NMR (deuteriochloroform): δ 13.0, 13.1, 41.7, 43.6, 53.2, 53.3, 67.3, 67.7, 92.7, 92.8, 110.0, 124.2, 124.9, 128.7, 128.9, 129.0, 129.2, 129.7, 130.9, 131.1, 133.7, 147.6, 155.9, 162.3, 169.5, 170.4; ms: (electron spray+) *m*/*z* 438.1 (M^+ + 1). *Anal*. Calcd for $C_{22}H_{19}N_3O_7$: C, 60.41; H, 4.38; N, 9.61. Found: C, 60.63; H, 4.47; N, 9.49.

Methyl 5-[acetoxy-(5-methyl-3-phenylisoxazol-4-yl)-methyl]-3-(2-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (5b). This compound was obtained in 83% as a pale yellow solid, mp. 74–76°C; IR (potassium bromide): 1752 (CO_2Me and OAc) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.19 (s, 3H, $OCOCH_3$), 2.26 (s, 3H, $OCOCH_3$), 2.72 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 3.26–3.50 (m, 4H, 2 × CH_2), 3.78 (s, 6H, 2 ×

CO_2CH_3), 6.37 (s, 1H, CHOAc), 6.42 (s, 1H, CHOAc), 7.12 (d, 1H, ArH, J = 7.6 Hz), 7.47–7.54 (m, 7H, 2 × 3ArH and ArH), 7.62–7.73 (m, 8H, 2 × 4ArH), 8.08 (d, 2H, 2 × 1ArH, J = 7.6 Hz); ^{13}C NMR (deuteriochloroform): δ 13.5, 13.7, 20.9, 21.0, 43.9, 44.1, 53.3, 53.8, 68.7, 69.3, 91.2, 91.5, 108.0, 108.7, 124.4, 125.4, 129.2, 129.6, 129.9, 130.3, 131.4, 131.7, 134.1, 134.3, 147.8, 148.2, 155.6, 162.2, 162.6, 169.7, 170.0, 171.7, 172.0; ms: (electron spray+) m/z 480.1 (M^+ + 1). *Anal*. Calcd for $C_{24}H_{21}N_3O_8$: C, 60.12; H, 4.41; N, 8.76. Found: C, 59.98; H, 4.53; N, 8.69.

Methyl 5-[hydroxy(3-phenylisoxazol-5-yl)methyl]-3-(2-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (9a). This compound was obtained in 82% as yellow oil; IR (neat): 1744 (CO_2Me), 3336 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.64–3.85 (m, 4H, 2 × CH_2), 3.89 (s, 3H, CO_2CH_3), 3.93 (s, 3H, CO_2CH_3), 5.47 (s, 1H, C*H*OH), 5.56 (s, 1H, C*H*OH), 6.75 (s, 1H, =CH), 6.78 (s, 1H, =CH), 7.46–7.52 (m, 6H, 2 × 3ArH), 7.58–7.72 (m, 4H, 2 × 2ArH), 7.78–8.04 (m, 6H, 2 × 3ArH), 8.06–8.09 (m, 2H, 2 × 1ArH); ^{13}C NMR (deuteriochloroform): δ 41.7, 43.9, 53.9, 54.0, 68.7, 69.0, 90.6, 91.5, 102.2, 124.4, 125.2, 127.3, 128.8, 129.4, 130.5, 130.6, 131.5, 131.6, 134.0, 134.2, 148.2, 156.6, 162.9, 169.6, 169.9; ms: (electron spray+) m/z 424.0 (M^+ + 1). *Anal*. Calcd for $C_{21}H_{17}N_3O_7$: C, 59.57; H, 4.05; N, 9.93. Found: C, 59.38; H, 4.17; N, 10.01.

Methyl 5-[(acetyloxy)(3-phenylisoxazol-5-yl)methyl]-3-(2-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (9b). This compound was obtained in 86% as yellow oil; IR (neat): 1757 (CO_2Me and OAc) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.20 (s, 3H, $OCOCH_3$), 2.25 (s, 3H, $OCOCH_3$), 3.72–4.02 (m, 10H, 2 × CH_2 and 2 × CO_2CH_3), 6.62 (s, 1H, CHOAc), 6.70 (s, 1H, CHOAc), 6.72 (s, 1H, =CH), 6.83 (s, 1H, =CH), 7.46–7.48 (m, 6H, 2 × 3ArH), 7.64–7.70 (m, 4H, 2 × 2ArH), 7.77–8.05 (m, 6H, 2 × 3ArH), 8.10–8.13 (m, 2H, 2 × 1ArH); ^{13}C NMR (deuteriochloroform): δ 21.0, 21.4, 42.4, 43.4, 54.1, 54.2, 67.8, 89.1, 90.0, 103.5, 103.9, 124.4, 124.5, 125.4, 127.2, 127.3, 128.6, 128.8, 129.4, 130.7, 130.8, 131.6, 134.1, 134.2, 148.2, 156.1, 156.2, 163.0, 166.1, 166.3, 168.3, 168.9, 169.5, 169.6, 171.5; ms: (electron spray+) m/z 466.0 (M^+ + 1). *Anal*. Calcd for $C_{23}H_{19}N_3O_8$: C, 59.36; H, 4.11; N, 9.03. Found: C, 59.21; H, 4.01; N, 9.12.

Methyl 3-(2-nitrophenyl)-5-[(3-phenylisoxazol-5-yl)methyl]-4,5-dihydroisoxazole-5-carboxylate (9c). This compound was obtained in 87% as brown oil; IR (neat): 1743 (CO_2Me) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.45 (d, 1H, 1H of CH_2, J = 17.4 Hz), 3.64 (s, 2H, CH_2), 3.85 (d, 1H, 1H of CH_2, J = 17.4 Hz), 3.91 (s, 3H, CO_2CH_3), 6.62 (s, 1H, =CH), 7.45–7.48 (m, 4H, ArH), 7.58–7.72 (m, 2H, ArH), 7.79–7.81 (m, 2H, ArH), 8.11 (d, 1H, ArH, J = 7.3 Hz); ^{13}C NMR (deuteriochloroform): δ 33.9, 45.6, 54.0, 88.1, 102.8, 124.6, 125.4, 127.3, 129.1, 129.4, 130.6, 131.5, 131.6, 134.2, 148.1, 156.2, 163.2, 167.4, 170.6; ms: (electron spray+) m/z 408.1 (M^+ + 1). *Anal*. Calcd for $C_{21}H_{17}N_3O_6$: C, 61.91; H, 4.21; N, 10.31. Found: C, 62.13; H, 4.12; N, 10.39.

Methyl 5-{hydroxy[3-(4-methylphenyl)isoxazol-5-yl]methyl}-3-(2-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (10a). This compound was obtained in 89% as pale yellow oil; IR (neat): 1742 (CO_2Me), 3371 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.40 (s, 6H, 2 × $ArCH_3$), 3.63–3.84 (m, 4H, 2 × CH_2), 3.88 (s, 3H, CO_2CH_3), 3.93 (s, 3H, CO_2CH_3), 5.46 (s, 1H, C*H*OH), 5.55 (s, 1H, C*H*OH), 6.72 (s, 1H, =CH), 6.74 (s, 1H, =CH), 7.24–7.28 (m, 4H, 2 × 2ArH), 7.48–7.51 (m, 2H, 2 × 1ArH), 7.61–7.71 (m, 8H, 2 × 4ArH), 8.05–8.09 (m, 2H, 2 × 1ArH); ^{13}C NMR (deuteriochloroform): δ 21.8, 41.7, 43.9, 53.9, 54.0, 68.7, 69.0, 90.6, 91.5, 102.1, 102.2, 124.5, 125.3, 125.9, 126.1, 127.2, 130.0, 131.5, 131.6, 134.0, 134.2, 140.8, 148.1, 156.6, 162.8, 169.3, 169.6, 170.3; ms: (electron spray+) m/z 438.1 (M^+ + 1). *Anal*. Calcd for $C_{22}H_{19}N_3O_7$: C, 60.41; H, 4.38; N, 9.61. Found: C, 60.58; H, 4.29; N, 9.70.

Methyl 5-[hydroxy-(3-phenylisoxazol-5-yl)-methyl]-3-(3-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (11a). This compound was obtained in 79% as a pale yellow solid, mp 138–140°C; IR (potassium bromide): 1744 (CO_2Me), 3421 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.68–3.91 (m, 4H, 2 × CH_2), 3.92 (s, 3H, CO_2CH_3), 3.93 (s, 3H, CO_2CH_3), 5.51 (s, 1H, C*H*OH), 5.58 (s, 1H, C*H*OH), 7.08 (s, 1H, =CH), 7.14 (s, 1H, =CH), 7.38–7.42 (m, 4H, 2 × 2ArH), 7.48–7.54 (m, 6H, 2 × 3ArH), 7.61–7.66 (m, 4H, 2 × 2ArH), 7.93–7.99 (m, 2H, 2 × 1ArH), 8.03–8.05 (m, 2H, 2 × 1ArH); ^{13}C NMR (deuteriochloroform): δ 42.3, 43.6, 53.9, 69.2, 91.2, 91.9, 104.3, 124.7, 125.3, 126.3, 127.6, 129.9, 131.5, 132.3, 134.0, 148.0, 148.2, 156.6, 162.6, 167.2, 169.9, 170.3; ms: (electron spray+) m/z 424.1 (M^+ + 1). *Anal*. Calcd for $C_{21}H_{17}N_3O_7$: C, 59.57; H, 4.05; N, 9.93. Found: C, 59.69; H, 4.19; N, 9.84.

Methyl 5-[hydroxy-(3-phenylisoxazol-5-yl)-methyl]-3-(4-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (12a). This compound was obtained in 79% as pale yellow oil; IR (neat): 1742 (CO_2Me), 3464 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.71 (d, 1H, 1H of CH_2, J = 17.1 Hz), 3.83–3.95 (m, 9H, CH_2, 1H of CH_2 and 2 × CO_2CH_3), 5.49 (s, 1H, C*H*OH), 5.58 (s, 1H, C*H*OH), 6.76 (s, 1H, =CH), 6.79 (s, 1H, =CH), 7.46–7.53 (m, 8H, 2 × 4ArH), 7.61–7.72 (m, 4H, 2 × 2ArH), 7.79–7.82 (m, 4H, 2 × 2ArH), 8.08–8.13 (m, 2H, 2 × 1ArH); ^{13}C NMR (deuteriochloroform): δ 41.7, 43.6, 53.8, 54.1, 68.9, 69.1, 90.6, 91.3, 102.6, 103.1, 124.5, 124.7, 125.4, 127.0, 128.8, 129.2, 130.5, 130.7, 131.4, 131.7, 134.1, 134.3, 148.2, 156.9, 163.7, 169.9, 170.3; ms: (electron spray+) m/z 424.1 (M^+ + 1). *Anal*. Calcd for $C_{21}H_{17}N_3O_7$: C, 59.57; H, 4.05; N, 9.93. Found: C, 59.43; H, 3.89; N, 9.97.

Methyl 5-{hydroxy[3-(4-methylphenyl)isoxazol-5-yl]methyl}-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (17). This compound was obtained in 85% as a white solid, mp. 118–120°C; IR (potassium bromide): 1744 (CO_2Me), 3438 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.40 (s, 6H, 2 × $ArCH_3$), 3.67–3.95 (m, 10H, 2 × CH_2 and 2 × CO_2CH_3), 5.55 (s, 1H, C*H*OH), 5.56 (s, 1H, C*H*OH), 6.68 (s, 1H, =CH), 6.69 (s, 1H, =CH), 7.24–7.28 (m, 6H, 2 × 3ArH), 7.37–7.43 (m, 4H, 2 × 2ArH), 7.15–7.19 (m, 2H, 2 × 1ArH), 7.63–7.70 (m, 6H, 2 × 3ArH); ^{13}C NMR (deuteriochloroform): δ 21.8, 21.9, 38.9, 41.9; 53.8, 68.9, 69.0, 90.0, 91.0, 102.0, 126.0, 127.2, 127.4, 128.6, 128.9, 129.2, 130.1, 131.2, 140.8, 141.3, 157.9, 162.8, 169.4, 169.7; ms: (electron spray+) m/z 393.1 (M^+ + 1). *Anal*. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14. Found: C, 67.47; H, 5.01; N, 7.21.

2-[3-(2-Nitrophenyl)-4,5-dihydroisoxazol-5-yl]-1-(3-phenylisoxazol-5-yl)ethan-1-ol (23). This compound was obtained in 69% as yellow oil; IR (neat): 3414 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.38–2.56 (m, 2H, CH_2), 3.00–3.14 (m, 1H, 1H of CH_2), 3.37–3.46 (m, 1H, 1H of CH_2), 5.01–5.28 (m, 1H, C*H*OH), 5.22–5.25 (m, 1H, C*H*CH_2), 6.62 (s, 1H, =CH), 7.44–7.46 (m, 3H, ArH), 7.57–7.70 (m, 3H, ArH), 7.79–7.82 (m, 2H, ArH), 8.06–8.09 (m, 1H, ArH); ^{13}C NMR

(deuteriochloroform): δ 40.7, 42.9, 65.3, 78.4, 99.5, 124.9, 125.4, 126.8, 128.8, 129.0, 130.1, 130.8, 131.0, 141.6, 156.0, 162.4, 174.6; ms: (electron spray+) *m/z* 380.0 ($M^+ + 1$). *Anal*. Calcd for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.49; H, 4.47; N, 11.34.

1-[3-(4-Methylphenyl)isoxazol-5-yl]-2-[3-(2-nitrophenyl)-4,5-dihydroisoxazol-5-yl]ethan-1-ol (24). This compound was obtained in 74% as pale yellow oil; IR (neat): 3382 (OH) cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.28–2.49 (m, 5H, CH_2 and $ArCH_3$), 2.97–3.18 (m, 1H, 1H of CH_2), 3.35–3.51 (m, 1H, 1H of CH_2), 5.01–5.16 (m, 1H, C*H*OH), 5.21–5.24 (m, 1H, C*H*CH_2), 6.60 (s, 1H, =CH), 7.24–7.28 (m, 1H, ArH), 7.55–7.61 (m, 2H, ArH), 7.62–7.72 (m, 3H, ArH), 8.08 (d, 2H, ArH, *J* = 7.7 Hz); ^{13}C NMR (deuteriochloroform): δ 21.7, 40.9, 41.3, 64.8, 79.5, 99.6, 125.0, 125.3, 126.5, 128.3, 129.2, 130.3, 130.6, 131.4, 141.2, 157.1, 162.1, 174.3; ms: (electron spray+) *m/z* 394.0 ($M^+ + 1$). *Anal*. Calcd for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68. Found: C, 63.91; H, 5.03; N, 10.47.

2-(3-Phenyl-4,5-dihydroisoxazol-5-yl)-1-(3-phenylisoxazol-5-yl)ethan-1-ol (27). This compound was obtained in 66% as a white solid, mp 135–137°C; IR (potassium bromide): 3380 (OH) cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.31–2.38 (m, 2H, CH_2), 3.10–3.20 (m, 1H, 1H of CH_2), 3.52–3.61 (m, 1H, 1H of CH_2), 4.98–5.16 (m, 1H, C*H*OH), 5.25–5.28 (m, 1H, C*H*CH_2), 6.60 (d, 1H, =CH, *J* = 2.1 Hz), 7.41–7.48 (m, 5H, ArH), 7.67–7.70 (m, 3H, ArH); 7.80–7.83 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 40.8, 41.3, 64.8, 77.9, 99.7, 126.9, 127.0, 128.79, 129.0, 129.3, 129.4, 130.3, 130.5, 130.6, 157.3, 162.6, 174.8; ms: (electron spray+) *m/z* 335.0 ($M^+ + 1$). *Anal*. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.92; H, 5.21; N, 8.55.

General procedure for the synthesis of compounds 3a–c, 6a–b, 13a–c, 14–16a, 18, 25–26, and 28: as exemplified for the compound 3a. A mixture of compound **2a** (1.5 g, 3.56 mmol) and Raney-Ni (100 mg wet) in methanol (10 mL) was subjected to hydrogenation in the Parr assembly at 40 psi. The reaction was allowed to continue for 3 h. Thereafter, the catalyst was removed by filtration of the reaction mixture through a celite bed with methanol. The filtrate was evaporated to obtain an oily residue, which was taken in ethyl acetate (2 × 20 mL) and washed with water (30 mL). The organic layers were collected, dried over anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo* to obtain a crude oily product, which was purified by column chromatography over silica gel (60–120 mesh). Elution with hexane: ethyl acetate (70:30, v/v) gave 0.93 g (67%) of compound **3a** as a brown solid.

The Pd-on-carbon-promoted hydrogenations were performed in similar fashion on a Parr assembly.

Methyl 3-(2-aminophenyl)-5-[hydroxy(phenylisoxazol-3-yl)methyl]-4,5-dihydroisoxazole-5-carboxylate (3a). Mp 83–85°C; IR (potassium bromide): 1745 (CO_2Me), 3352 (NH), 3461 (OH) cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.81 (d, 1H, 1H of CH_2, *J* = 17.1 Hz), 3.88 (s, 3H, CO_2CH_3), 3.98 (d, 1H, 1H of CH_2, *J* = 17.1 Hz), 5.54 (s, 1H, CHOH), 6.67–6.74 (m, 3H, =CH and ArH), 7.16–7.24 (m, 2H, ArH), 7.45–7.48 (m, 3H, ArH), 7.78–7.83 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 42.5, 53.9, 69.2, 91.8, 99.4, 125.3, 126.3, 127.4, 128.5, 129.4, 130.9, 131.5, 134.0, 148.1, 156.6, 162.8, 170.0, 170.9; ms: (electron spray+) *m/z* 394.2 ($M^+ + 1$). *Anal*. Calcd for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68. Found: C, 63.98; H, 4.95; N, 10.73.

Methyl 5-[acetoxy-(5-phenylisoxazol-3-yl)-methyl]-3-(2-amino-phenyl)-4,5-dihydromisoxazole-5-carboxylate (3b). This compound was obtained in 63% as yellow oil; IR (neat): 1743 (CO_2Me), 3358 (NH) cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.17 (s, 3H, $OCOCH_3$), 3.53–3.67 (m, 3H, CH_2 and 1H of CH_2), 3.86 (s, 3H, CO_2CH_3), 4.03 (d, 1H, 1H of CH_2, *J* = 17.0 Hz), 5.59 (s, 2H, NH_2), 6.56 (s, 1H, =CH), 6.69–6.75 (m, 2H, ArH), 7.12–7.23 (m, 2H, ArH), 7.45–7.47 (m, 3H, ArH), 7.78–7.79 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 34.0, 44.8, 53.8, 85.6, 102.4, 110.8, 116.4, 117.0, 127.2, 129.3, 130.1, 130.5, 131.7, 147.3, 158.5, 163.1, 167.6, 171.1; ms: (electron spray+) *m/z* 436.1 ($M^+ + 1$). *Anal*. Calcd for $C_{23}H_{21}N_3O_6$: C, 63.44; H, 4.86; N, 9.65. Found: C, 63.68; H, 5.07; N, 9.56.

Methyl 3-(2-amino-phenyl)-5-[hydroxy-(5-methyl-3-phenylisoxazol-4-yl)-methyl]-4,5-dihydro-isoxazole-5-carboxylate (6a). This compound was obtained in 66% as yellow oil; IR (neat): 1731 (CO_2Me), 3466 (NH and OH) cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.66 (s, 3H, CH_3), 3.21 (d, 1H, 1H of CH_2, *J* = 17.0 Hz), 3.44 (d, 1H, 1H of CH_2, *J* = 17.0 Hz), 3.60 (s, 3H, CO_2CH_3), 5.40 (s, 1H, C*H*OH), 6.64–6.74 (m, 3H, ArH), 7.15–7.21 (m, 1H, ArH), 7.50–7.54 (m, 3H, ArH), 7.55–7.59 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 13.2, 30.3, 43.1, 53.7, 69.4, 88.7, 107.9, 110.1, 117.4, 117.9, 129.1, 129.5, 130.6, 131.7, 133.0, 147.1, 157.4, 163.2, 169.9, 170.6; ms: (electron spray+) *m/z* 408.1 ($M^+ + 1$). *Anal*. Calcd for $C_{22}H_{21}N_3O_5$: C, 64.86; H, 5.20; N, 10.31. Found: C, 64.98; H, 5.08; N, 10.43.

Methyl 5-[acetoxy-(5-methyl-3-phenylisoxazol-4-yl)-methyl]-3-(2-amino-phenyl)-4,5-dihydro-isoxazole-5-carboxylate (6b). This compound was obtained in 92% as a white solid, mp. 180–182°C; IR (potassium bromide) 1756 (CO_2Me and OAc), 3346 (NH) cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.16 (s, 3H, $OCOCH_3$), 2.70 (s, 3H, CH_3), 3.00 (d, 1H, 1H of CH_2, *J* = 17.0 Hz), 3.39 (d, 1H, 1H of CH_2, *J* = 17.0 Hz), 3.77 (s, 3H, CO_2CH_3), 5.49 (s, 2H, NH_2), 6.38 (s, 1H, CHOAc), 6.62–6.71 (m, 3H, ArH), 7.15–7.20 (m, 1H, ArH), 7.53–7.55 (m, 3H, ArH), 7.59–7.63 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 13.4, 20.9, 30.1, 43.4, 53.7, 69.6, 88.9, 107.9, 110.1, 116.4, 116.7, 129.4, 129.6, 130.4, 131.8, 132.9, 147.2, 157.4, 162.5, 169.7, 170.6, 171.8; ms: (electron spray+) *m/z* 449.9 ($M^+ + 1$). HR-EIMS Calcd for $C_{24}H_{23}N_3O_6$: 449.1587. Found: 449.1566.

Methyl 3-(2-aminophenyl)-5-[hydroxy(3-phenylisoxazol-5-yl)methyl]-4,5-dihydroisoxazole-5-carboxylate (13a). This compound was obtained in 67% as brown oil; IR (neat): 1742 (CO_2Me), 3350 (NH), 3464 (OH) cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.77–3.94 (m, 5H, CH_2 and CO_2CH_3), 5.54 (brs, 3H, C*H*OH and NH_2), 6.67–6.74 (m, 3H, =CH and ArH), 7.16–7.23 (m, 2H, ArH), 7.45–7.46 (m, 3H, ArH), 7.76–7.79 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 40.6, 53.9, 69.0, 89.0, 102.0, 110.9, 116.5, 117.2, 127.3, 128.9, 129.4, 130.3, 130.7, 131.8, 147.2, 159.1, 162.8, 169.6, 170.0; ms: (electron spray+) *m/z* 394.1 ($M^+ + 1$). *Anal*. Calcd for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68. Found: C, 64.31; H, 4.72; N, 10.79.

Methyl 3-(2-aminophenyl)-5-{hydroxy[3-(4-methylphenyl) isoxazol-5-yl]methyl}-4,5-dihydroisoxazole-5-carboxylate (14a). This compound was obtained in 63% as colorless oil; IR (neat): 1741 (CO_2Me), 3352 (NH), 3461(OH) cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.40 (s, 3H, $ArCH_3$), 3.78 (d,

1H, 1H of CH_2, J = 17.1 Hz), 3.87 (s, 3H, CO_2CH_3), 3.97 (d, 1H, 1H of CH_2, J = 17.1 Hz), 5.53 (brs, 3H, C*H*OH and NH_2), 6.68–6.74 (m, 3H, =CH and ArH), 7.16–7.24 (m, 4H, ArH), 7.69 (d, 2H, ArH, J = 7.8 Hz); ^{13}C NMR (deuteriochloroform): δ 21.8, 40.5, 53.9, 69.0, 89.1, 101.9, 110.9, 116.5, 117.2, 126.0, 127.2, 130.1, 130.3, 131.7, 140.8, 147.2, 159.1, 162.8, 169.5, 170.0; ms: (electron spray+) *m*/*z* 408.1 ($M^+ + 1$); *Anal*. Calcd for $C_{22}H_{21}N_3O_5$: C, 64.86; H, 5.20; N, 10.31. Found: C, 64.67; H, 5.09; N, 10.43.

Methyl 3-(3-aminophenyl)-5-[hydroxy-(3-phenylisoxazol-5-yl)-methyl]-4,5-dihydro-isoxazole-5-carboxylate (15a). This compound was obtained in 73% as a brown solid, mp. 114–116°C; IR (potassium bromide): 1721 (CO_2Me), 3321 (NH), 3456 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.72–3.88 (m, 5H, CH_2 and CO_2CH_3), 5.31 (s, 1H, C*H*OH), 5.46 (s, 2H, NH_2), 6.62–6.67 (m, 2H, =CH and ArH), 6.87–6.93 (m, 2H, ArH), 7.06–7.12 (m, 1H, ArH), 7.31–7.38 (m, 3H, ArH), 7.69–7.70 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 40.5, 52.0, 67.6, 88.1, 100.2, 111.7, 116.2, 116.4, 125.6, 127.6, 127.7, 128.4, 128.8, 145.4, 155.9, 161.1, 168.3; ms: (electron spray+) *m*/*z* 394.1 ($M^+ + 1$); *Anal*. Calcd for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68. Found: C, 64.37; H, 4.98; N, 10.49.

Methyl 3-(4-aminophenyl)-5-[hydroxy-(3-phenylisoxazol-5-yl)-methyl]-4,5-dihydro-isoxazole-5-carboxylate (16a). This compound was obtained in 69% as yellow oil; IR (neat): 1745 (CO_2Me), 3345 (NH), 3442 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.83 (d, 2H, 1H of CH_2, J = 17.0 Hz), 3.89 (s, 3H, CO_2CH_3), 4.00 (d, 2H, 1H of CH_2, J = 17.0 Hz), 5.55 (s, 1H, C*H*OH), 6.73–6.75 (m, 3H, =CH and ArH), 7.19 (d, 2H, ArH, J = 7.5 Hz), 7.47–7.49 (m, 3H, ArH), 7.80–7.85 (m, 3H, ArH); ^{13}C NMR (deuteriochloroform): δ 41.3, 53.2, 67.9, 88.7, 101.4, 111.3, 115.1, 114.9, 125.4, 126.4, 127.0, 128.1, 128.4, 129.6, 144.7, 156.7, 161.8, 168.5, 170.2; ms: (electron spray+) *m*/*z* 394.2 ($M^+ + 1$). *Anal*. Calcd for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68. Found: C, 64.27; H, 4.73; N, 10.79.

3-[(Z)-4-Amino-1-hydroxy-4-(4-methylphenyl)-2-oxobut-3-enyl]-3-hydroxy-5-phenylpyrrolidin-2-one (18). This compound was obtained in 85% as a pale yellow solid, mp. 90–92°C; IR (potassium bromide): 1685 (CONH), 1721 (CO), 3426 (OH and NH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.42 (s, 6H, 2 × $ArCH_3$), 3.48 (d, 1H, 1H of CH_2, J = 17.1 Hz), 3.72 (d, 1H, 1H of CH_2, J = 17.1 Hz), 3.83–3.96 (m, 2H, CH_2), 4.26 (s, 2H, 2 × ArCH), 4.36 (brs, 1H, 1H of NH_2), 4.75 (s, 1H, C*H*OH), 4.82 (s, 1H, C*H*OH), 5.34 (brs, 1H, 1H of NH_2), 5.64 (brs, 1H, 1H of NH_2), 5.67 (brs, 1H, 1H of NH_2), 5.74 (s, 1H, =CH), 5.81 (s, 1H, =CH), 7.37–7.51 (m, 14H, 2 × 7ArH), 7.60–7.72 (m, 4H, 2 × 2ArH), 9.89 (brs, 1H, NH), 8.96 (brs, 1H, NH); ^{13}C NMR (deuteriochloroform): δ 21.5, 21.8, 33.4, 33.5, 39.9, 41.3, 89.4, 89.5, 93.9, 94.1, 103.1, 103.4, 126.1, 126.3, 127.4, 127.8, 128.2, 128.8, 129.2, 130.3, 131.2, 140.4, 141.5, 157.6, 157.7, 162.4, 162.7, 179.3, 179.5, 190.4, 190.6; ms: (electron spray+) *m*/*z* 367.1 ($M^+ + 1$). *Anal*. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.69; H, 6.19; N, 7.57.

2-[3-(2-Aminophenyl)-4,5-dihydroisoxazol-5-yl]-1-(3-phenylisoxazol-5-yl)ethan-1-ol (25). This compound was obtained in 63% as a yellow solid, mp 110–112°C; IR (potassium bromide): 3431 (OH and NH_2) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.27–2.36 (m, 2H, CH_2), 3.16–3.29 (m, 1H, 1H of CH_2), 3.60–3.69 (m, 1H, 1H of CH_2), 4.90–4.96 (m, 1H, C*H*OH), 5.24–5.26 (m, 1H, C*H*CH_2), 6.62 (d, 1H, =CH, J = 3.5 Hz), 6.70–6.77 (m, 2H, ArH), 7.15–7.23 (m, 2H, ArH); 7.46–7.48 (m, 3H, ArH), 7.80–7.82 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 40.8, 41.2, 64.9, 78.6, 99.6, 111.8, 116.2, 116.6, 117.0, 126.1, 126.9, 129.8, 131.0, 131.3, 140.6, 147.1, 162.5, 174.5; ms: (electron spray+) *m*/*z* 350.1 ($M^+ + 1$). *Anal*. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.62; H, 5.19; N, 12.28.

2-[3-(2-Aminophenyl)-4,5-dihydroisoxazol-5-yl]-1-[3-(4-methylphenyl)isoxazol-5-yl]ethan-1-ol (26). This compound was obtained in 62% as a brown solid mp 158–160°C; IR (potassium bromide): 3374 (OH and NH_2) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.24–2.33 (m, 2H, CH_2), 2.40 (s, 3H, $ArCH_3$), 3.19–3.29 (m, 1H, 1H of CH_2), 3.56–3.69 (m, 1H, 1H of CH_2), 4.63–4.94 (m, 1H, C*H*OH), 5.21–5.24 (m, 1H, C*H*CH_2), 5.63 (brs, 2H, NH_2), 6.58 (d, 1H, =CH, J = 1.2 Hz), 6.66–6.76 (m, 2H, ArH), 7.13–7.19 (m, 2H, ArH); 7.22–7.28 (m, 2H, ArH), 7.69 (d, 2H, ArH, J = 8.0 Hz); ^{13}C NMR (75 MHz, deuteriochloroform): δ= 21.7, 40.6, 42.5, 65.2, 78.0, 99.7, 111.6, 116.1, 116.8, 116.9, 126.2, 127.0, 129.9, 131.1, 131.2, 140.5, 147.0, 158.9, 162.6, 173.9; ms: (electron spray+) *m*/*z* 364.1 ($M^+ + 1$). HR-EIMS Calcd for $C_{21}H_{21}N_3O_3$: 363.1583. Found: 363.1577.

1,8-Diamino-4,6-dihydroxy-1,8-diphenyloct-1-en-3-one (28). This compound was obtained in 63% as a brown solid, mp 118–120°C; IR (potassium bromide): 3410 (OH and NH_2) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.71 (brs, 1H, OH), 1.79–2.06 (m, 4H, 2 × CH_2), 3.71 (brs, 5H, OH and 2 × NH_2), 4.15–4.22 (m, 1H, C*H*OH), 4.37–4.39 (m, 1H, C*H*OH), 4.48–4.50 (m, 1H, C*H*NH_2), 5.53 (s, 1H, =CH), 7.33–7.57 (m, 10H, ArH); ^{13}C NMR (deuteriochloroform): δ 29.6, 30.7, 49.5, 52.9, 90.3, 126.4, 127.6, 128.6, 128.9, 129.3, 129.6, 129.9, 130.0, 134.2, 175.2; ms: (electron spray+) *m*/*z* 341.1 ($M^+ + 1$). *Anal*. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.75; H, 7.03; N, 8.31.

(Z)-4-Amino-1-hydroxy-4-phenylbut-3-en-2-one (30). This compound was obtained in 67% as yellow oil; IR (neat): 1703 (CO), 3407 (OH and NH_2) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.61 (brs, 1H, OH), 4.26 (s, 2H, CH_2), 5.36 (s, 1H, =CH), 7.40–7.61 (m, 5H, ArH), 9.69 (brs, 2H, NH_2); ms: (electron spray+) *m*/*z* 178.1 ($M^+ + 1$). *Anal*. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.83; H, 6.41; N, 7.62.

General procedure for the synthesis of compounds 21–22: as exemplified for the compound 21. To the stirred suspension of Mg (0.42 g, 17.34 mmol) in anhydrous diethyl ether (30 mL), allyl bromide (1.5 mL, 17.34 mmol) was added under nitrogen atmosphere at room temperature and the mixture was stirred for 1 h. Thereafter, the resulting Grignard reagent was added to the stirred solution of appropriate aldehydes from **19** (1.5 g, 8.67 mmol) in anhydrous diethyl ether (40 mL) dropwise *via* cannula under nitrogen atmosphere, and the reaction was continued for additional 5 h. After completion, the reaction mixture was decomposed with cold H_2O maintaining the pH at 5–6 with dil. HCl. The resulting mixture was extracted with diethyl ether (3 × 30 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, and evaporated to yield crude product, which was purified *via* silica gel chromatography using hexane: EtOAc (80:20, v/v) to afford 1.4 g (75%) of compound **21** as yellow oil.

1-(3-Phenylisoxazol-5-yl)but-3-en-1-ol (21). IR (neat): 3411 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.65–2.76

(m, 2H, CH_2CH), 4.94, 4.99 (dd, 1H, C*H*OH, J_1 = 6.7 Hz, J_2 = 16.7 Hz), 5.21–5.30 (m, 2H, =CH_2), 5.73–5.93 (m, 1H, =C*H*CH_2), 6.54 (d, 1H, =CH, J = 0.9 Hz), 7.42–7.49 (m, 3H, ArH), 7.78–7.82 (m, 2H, ArH); ^{13}C NMR (deuteriochloroform): δ 40.7, 66.9, 98.8, 120.6, 126.2, 126.7, 127.2, 129.4, 133.0, 141.3, 162.1, 174.7; ms: (electron spray+) *m/z* 216.1 (M^+ + 1). *Anal*. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.31; H, 5.97; N, 6.63.

1-[3-(4-Methylphenyl)isoxazol-5-yl]but-3-en-1-ol (22). This compound was obtained in 90% as pale yellow oil; IR (neat): 3384 (OH) cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.40 (s, 3H, ArCH_3), 2.65–2.75 (m, 2H, CH_2CH), 4.91–5.00 (m, 1H, C*H*OH), 5.20–5.30 (m, 2H, =CH_2), 5.73–5.90 (m, 1H, =C*H*CH_2), 6.51 (d, 1H, =CH, J = 1.0 Hz), 7.26 (d, 2H, ArH, J = 8.0 Hz), 7.69 (d, 2H, ArH, J = 8.0 Hz); ^{13}C NMR (deuteriochloroform): δ 21.7, 40.5, 66.6, 99.3, 120.1, 126.3, 127.0, 129.9, 132.7, 140.4, 162.5, 174.3; ms: (electron spray+) *m/z* 230.1 (M^+ + 1). *Anal*. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.19; H, 6.72; N, 6.01.

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REFERENCES AND NOTES

[1] (a) Claisen, L. Ber Dtsch Chem Ges 1891, 24, 3900; (b) Bianchi, G.; DeAmici, M. J Chem Soc Chem Commun 1978, 962; (c) Bode, J. W.; Hachisu, Y.; Matsuura, T.; Suzuki, K. Org Lett 2003, 5, 391; (d) Bode, J. W.; Uesuka, H.; Suzuki, K. Org Lett 2003, 5, 395; (e) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. Synthesis 1987, 857; (f) Li, C. S.; Lacasse, E. Tetrahedron Lett 2002, 43, 3565; (g) Jones, R. C. F.; Dunn, S. H.; Duller, K. A. M. J Chem Soc Perkin Trans 1 1996, 1319; (h) Kenar, J. A. J Am Oil Chem Soc 2003, 80, 1027; (i) Jones, R. C. F.; Bhalay, G.; Carter, P. A.; Duller, K. A. M.; Dunn, S. H. J Chem Soc Perkins Trans 1 1994, 2513; (j) Jones, R. C. F.; Bhalay, G.; Carter, P. A.; Duller, K. A. M.; Vulto, S. I. E. J Chem Soc Perkins Trans 1 1999, 765; (k) Jones, R. C. F.; Dawson, C. E.; O'Mahony, M. J. Synlett 1999, 873.

[2] Singh, V.; Madapa, S.; Yadav, G. P.; Maulik, P. R.; Batra, S. Synthesis 2006, 1995.

[3] Singh, V.; Batra, S. Tetrahedron 2008, 64, 2979.

[4] (a) Zhang, P.-Z.; Li, X.-L.; Chen, H.; Li, Y.-N.; Wang, R. Tetrahedron Lett 2007, 48, 7813; (b) Conti, P.; Caligiuri, A.; Pinto, A.; Roda, G.; Tamborini, L.; Nielsen, B.; Madsen, U.; Frydenvang, K.; Colombo, A.; Micheli, C. D. Eur J Med Chem 2007, 42, 1059; (c) Wityak, J.; Sielecki, T. M.; Pinto, D. J.; Emmett, G.; Sze, J. Y.; Liu, J.; Tobin, A. E.; Wang, S.; Jiang, B.; Ma, P.; Mousa, S. A.; Wexler, R. R.; Olson, R. E. J Med Chem 1997, 40, 50; (d) Yong, S. R.; Ung, A. T.; Pyne, S. G.; Skelton, B. W.; White, A. H. Tetrahedron 2007, 63, 5579; (e) Faulkner, J. Nat Prod Rep 2001, 18, 1; (f) Wright, A. D.; King, G. M.; Sticher, O. J Nat Prod 1990, 53, 1615; (g) Smallheer, J. M.; Weigelt, C. A.; Woerner, F. J.; Wells, J. S.; Daneker, W. F.; Mousa, S. A.; Wexler, R. R.; Jadhav, P. K. Bioorg Med Chem Lett 2004, 14, 383; (h) Encarnacion-Dimayuga, R.; Ramırez, M. R.; Luna-Herrera, J. Pharm Biol 2003, 41, 384; (i) Cue, D.; Southern, S. O.; Southern, P. J.; Prabhakar, J.; Lorelli, W.; Smallheer, J. M.; Mousa, S. A.; Cleary, P. P. Proc Natl Acad Sci USA 2000, 97, 2858; (j) Ogamino, T.; Obata, R.; Tomoda, H.; Nishiyama, S. Bull Chem Soc Jpn 2006, 79, 134; (k) Adamo, M. F. A.; Donati, D.; Duffy, E. F.; Sarti-Fantoni, P. J Org Chem 2005, 70, 8395.

[5] (a) Wasserman, H. H.; Wang, J. J Org Chem 1998, 63, 5581; (b) Compagnone, R. S.; Avila, R.; Suarez, A. I.; Abrams, O. V.; Rangel, H. R.; Arvelo, F.; Ivette Pina, C.; Merentes, E. J Nat Prod 1999, 62, 1443; (c) Goldenstein, K.; Fendert, T.; Proksch, P.; Winterfeldt, E. Tetrahedron 2000, 56, 4173; (d) Boehlow, T. R.; Jonathan Harburn, J.; Spilling, C. D. J Org Chem 2001, 66, 3111; (e) Takada, N.; Watanabe, R.; Suenaga, K.; Yamada, K.; Ueda, K.; Kitaa, M.; Uemuraa, D. Tetrahedron Lett 2001, 42, 5265; (f) Tabudravu, J. N.; Jaspars, M. J Nat Prod 2002, 65, 1798; (g) Harburn, J. J.; Rath, N. P.; Spilling, C. D. J Org Chem 2005, 70, 6398; (h) Ogamino, T.; Obata, R.; Nishiyama, S. Tetrahedron Lett 2006, 47, 727; (i) Sayed, K. A. E.; Bartyzel, P.; Shen, X.; Perry, T. L.; Zjawiony, J. K.; Hamann, M. T. Tetrahedron 2000, 56, 949.

[6] (a) Yamamoto, T.; Fujita, K.; Asari, S.; Chiba, A.; Kataba, Y.; Ohsumi, K.; Ohmuta, N.; Iida, Y.; Ijichi, C.; Iwayama, S.; Fukuchi, N.; Shoji, M. Bioorg Med Chem Lett 2007, 17, 3736; (b) Cheng, J.-F.; Chen, M.; Liu, B.; Hou, Z.; Arrhenius, T.; Nadzan, A. M. Bioorg Med Chem Lett 2006, 16, 695; (c) Shen, D.-M.; Shu, M.; Mills, S. G.; Chapman, K. T.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Siciliano, S. J.; Kwei, G. Y.; Carella, A.; Carver, G.; Holmes, K.; Schleif, W. A.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Millerd, M. D.; Eminid, E. A. Bioorg Med Chem Lett 2004, 14, 935; (d) Fader, L. D.; Carreira, E. M. Org Lett 2004, 6, 2485; (e) Conti, D.; Rodriquez, M.; Sega, A.; Taddei, M. Tetrahedron Lett 2003, 44, 5327; (f) Batt, D. G.; Houghton, G. C.; Daneker, W. F.; Jadhav, P. K. J Org Chem 2000, 65, 8100; (g) Martin, L.; Polo, C.; Ramos, V.; Torroba, T.; Marcaccini, S. Heterocycles 1993, 36, 2259; (h) Campbell, M. M.; Cosford, N. D. P.; Rae, D. R.; Sainsbury, M. J Chem Soc Perkin Trans 1 1991, 765; (i) Yamanaka, H.; Shiraiwa, M.; Sakamoto, T.; Konno, S. Chem Pharm Bull 1981, 29, 3548; (j) McKenzie, T. C. J Org Chem 1974, 39, 629.

[7] Roy, A. K.; Batra, S. Synthesis 2003, 1347.

[8] Roy, A. K.; Batra, S. Synthesis 2003, 2325.

[9] Patra, A.; Batra, S.; Kundu, B.; Joshi, B. S.; Roy, R.; Badhuri, A. P. Synthesis 2001, 276.

[10] Crystal data of compound **6b**: $C_{24}H_{23}N_3O_6$ (from methanol), M = 449.45, Orthorhombic, Pna2 (1), a = 18.34(3), b = 9.076 (214.746(2), c = 8.374(1) Å, V = 2264.7(6) Å^3, Z = 4, D_c = 1.318 g cm^{-3}, μ (Mo–K$_\alpha$) = 0.096 mm^{-1}, F (000) = 944, colorless block, dimension 0.275 mm × 0.25 mm × 0.15 mm, 2804 reflections measured (R_{int} = 0.0234), 2436 unique, wR_2 = 0.1112, conventional R = 0.0517 on F values of 1235 reflections with $I > 2\sigma(I)$, $(\Delta/\sigma)_{max}$ = 000), S = 0.999 for all data and 184 parameters. Unit cell determination and intensity data collection (2θ = 50°) was performed on a Bruker P4 diffractometer at 293 (2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS (Siemens Analytical X-ray Instrument: Madison, WI, USA, 1996) for data collection and data processing; SHELXTL-NT (Bruker AXS: Madison, Wisconsin, USA, 1997) for structure determination, refinements and molecular graphics. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposition no.: 715052). This is CDRI communication no. 7689.